Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. DOI: 10.1056/NEJMoa1400376

Supplementary Appendix

Supplement to: Byrd J.C., Brown J.R., O'Brien S. et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

Contents

Text S1. Eligibility Criteria Defining "Not Appropriate for Purine Analog Treatment"

Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog–based therapy, defined by at least one of the following criteria:

a) Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog–based therapy and anti-CD20–containing chemoimmunotherapy regimen after at least two cycles.

b) Age ≥70 years, or age ≥65 and the presence of comorbidities (Cumulative Illness Rating Scale [CIRS] ≥6 or creatinine clearance <70 ml/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog–based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent–based (or purine analog–based) anti-CD20 antibody–containing chemoimmunotherapy regimen. CIRS score can be determined using a web-based tool.

c) History of purine analog–associated autoimmune anemia or autoimmune thrombocytopenia.

d) Fluorescent hybridization showing del17p in ≥20% of cells (either at diagnosis or at any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided the patient has received at least one prior therapy.

Text S2. Participating Investigators

The study was conducted at 67 sites in nine countries, including the United States, Europe, and Australia. Dr. John Byrd, Dr. Jennifer Brown, Dr. Susan O'Brien, Dr. Jacqueline Barrientos, Dr. Neil Kay, Dr. Nishitha Reddy, Prof. Peter Hillmen, Dr. Steven Coutre, Dr. Constantine Tam, Dr. Stephen Mulligan, Dr. Ulrich Jaeger, Dr. Steve Devereux, Dr. Paul Barr, Dr. Richard Furman, Dr. Thomas Kipps, Prof. Florence Cymbalista, Dr. Chris Pocock, Dr. Patrick Thornton, Prof. Federico Caligaris-Cappio, Prof. Tadeusz Robak, Dr. Julio Delgado, Dr. Stephen Schuster, Dr. Marco Montillo, Dr. Anna Schuh, Dr. Sven de Vos, Dr. Devinder Gill, Dr. Adrian Bloor, Dr. Claire Dearden, Dr. Carol Moreno, Dr. Jeff Jones, , Dr. John Pagel, Dr. Richard Frank, Dr. Gavin Cull, Dr. Gabriel Etienne, Dr. Gianpietro Semenzato, Dr. Chris Fegan, Dr. Chris Fox, Dr. Mike Hamblin, Dr. Renate Walewska, Dr. Andrew Pettitt, Dr. Rajat Bannerji, Dr. Michael Williams, Dr. Olivier Tournhilac, Dr. Xavier Troussard, Dr. Sophie De Guibert, Prof. Andrzej Hellmann, Dr. Jose Antonio García Marco, Dr. Andrew Duncombe, Dr. Robert C. Hermann, Prof. Dr. Heinz Ludwig, Dr. Sonja Burgstaller, Prof. Werner Linkesch, Dr. Pierre Feugier, Dr. Beatrice Mahe, Dr. Armando Santoro, Dr. Roberto Marasca, Dr. Pau Abrisqueta, Dr. Michael O'Dwyer, Dr. Charles Schiffer, Dr. Maqbool Ahmed, Dr. Euardo Miranda, Dr. Richard Greil, Dr. Therese Aurran-Schlenitz, Dr. Phillipe Genet, Dr. José Rifón Roca, Dr. José Francisco Tomás Martínez, Prof. Elisabeth Vandenberghe.

Text S3. Funding Acknowledgements

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Figure S1. CONSORT Diagram.

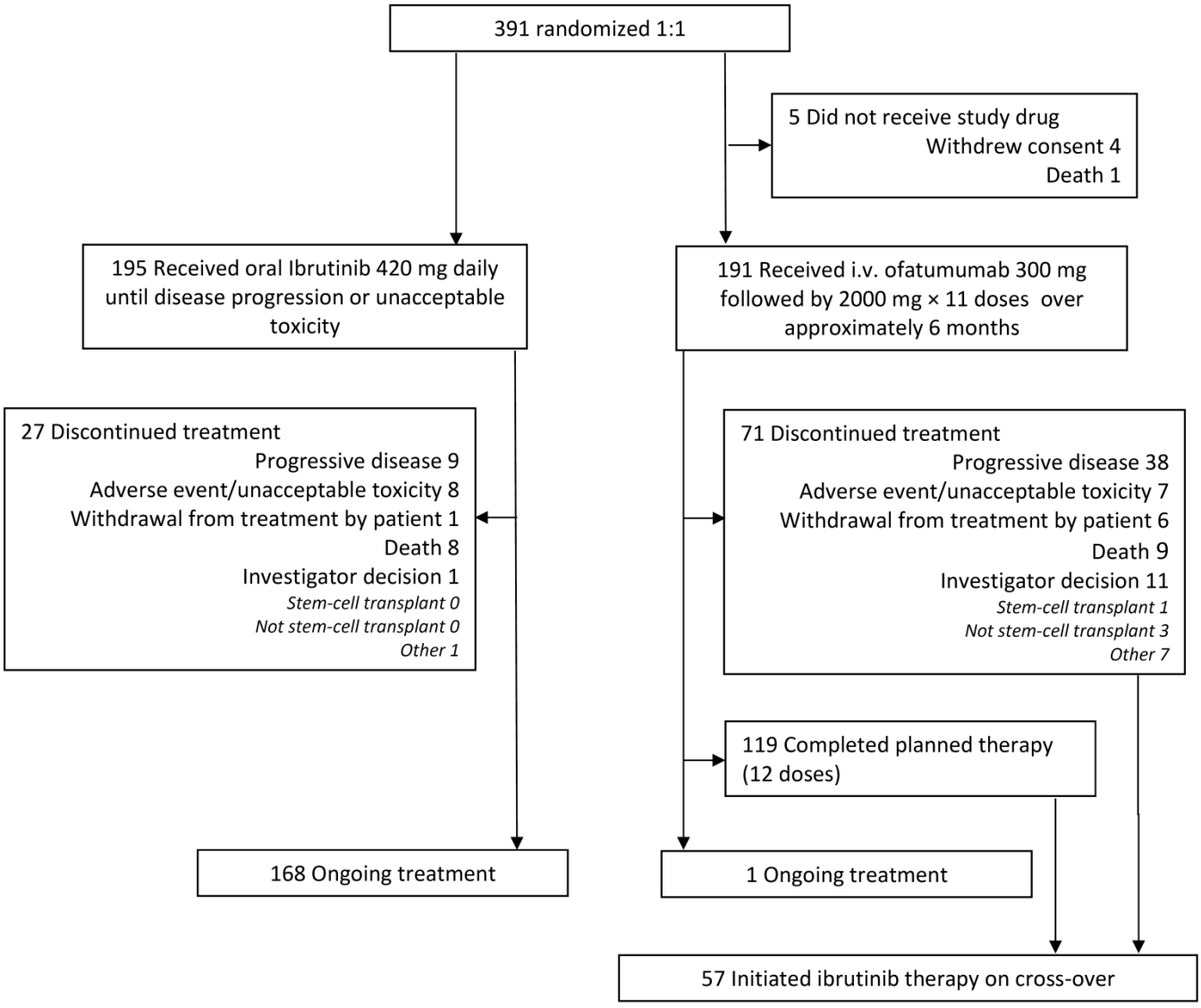


Figure S2. Overall Survival by Treatment Arm (Noncensored Analysis of ITT).

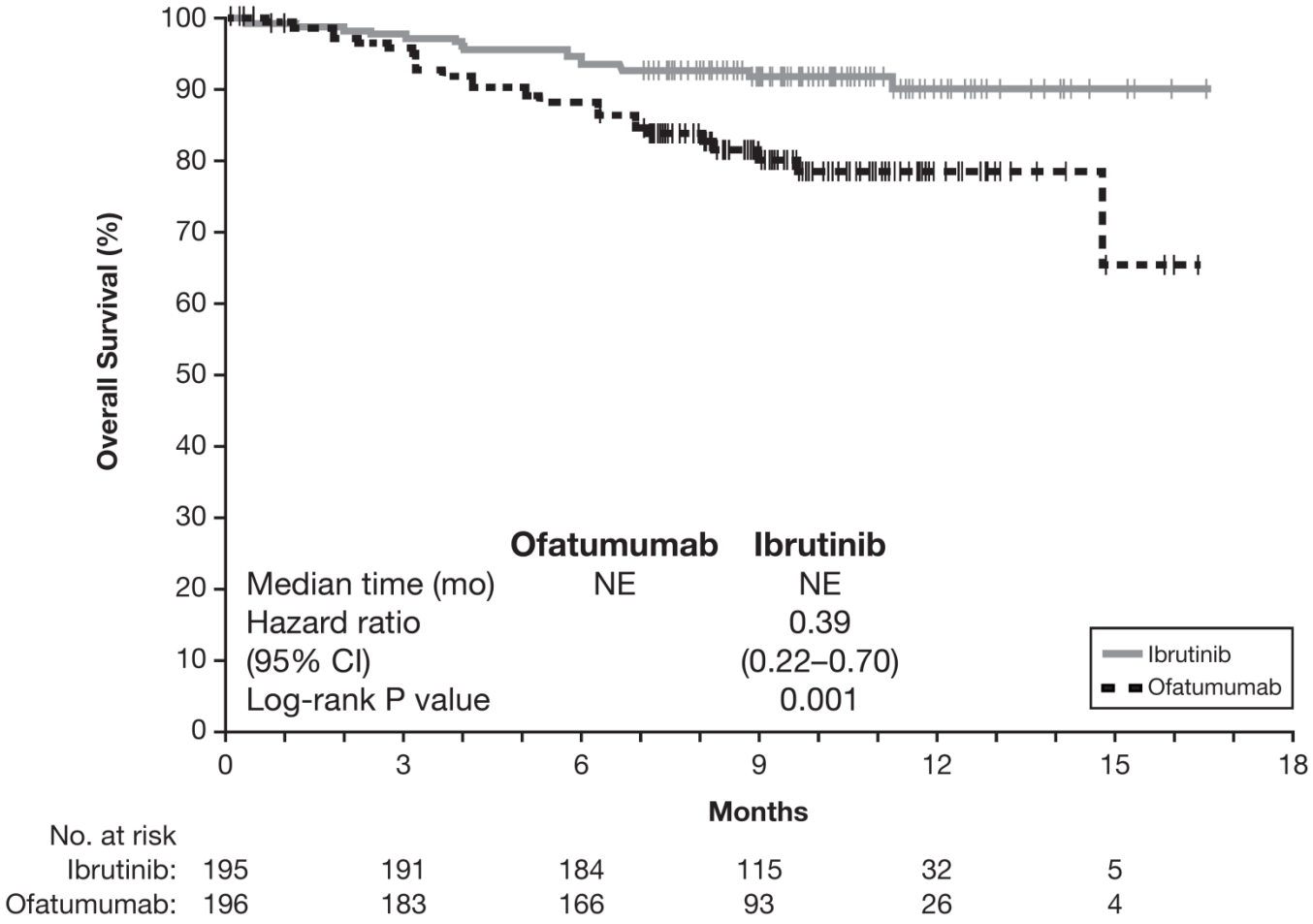
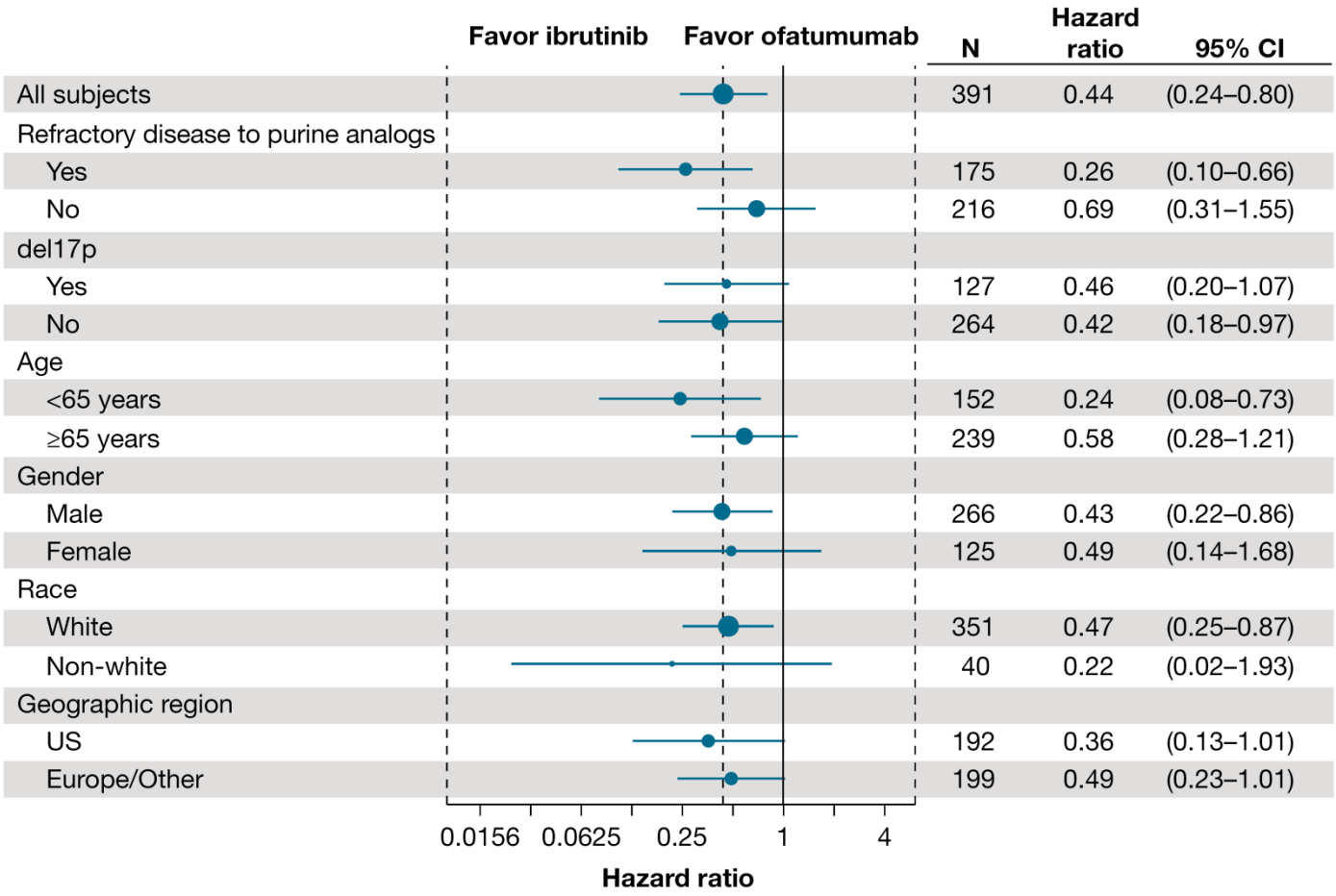


Figure S3. Forest Plot of Hazard Ratios for Overall Survival.



Logarithmic base 2.

Table S1 Criteria for Response Categories

Parameter	CR	PR	PD
Group A			
Lymphadenopathy[a]	None; ≤1.5cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50% or new hepatomegaly
Splenomegaly	None	Decrease ≥50%	Increase ≥50% or new splenomegaly
Blood lymphocytes	<4000/μL	Decrease ≥50% from baseline	Increase ≥50% over baseline[c]
Marrow[b]	Normocellular, <30% lymphocytes, no B lymphoid nodules, no clonal infiltrate. Hypocellular defines CRi		
Group B			
Platelet count	>100,000/μL	>100,000/μL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11 g/dL	>11g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophils	>1500/μL	>1500/μL or increase ≥50% over baseline	N/A

[a] Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node.

[b]This parameter is not relevant for the PD category unless confirming cytopenic progression.

[c]Patients with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease.

Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system.

CR: all of the criteria need to be met and patients have to lack disease related constitutional symptoms. Bone marrow and aspirate is required to confirm CR.

PR: all abnormal Group A criteria must be met plus 1 of the criteria from Group B must be met. Note if all PR criteria with the exception of ALC are met this is consistent with a PR with lymphocytosis.

SD: the absence of PD and the failure to achieve a CR, CRi, nPR, PR, or PR with lymphocytosis.

PD: at least 1 of the above criteria from Group A or B are met or development of transformation to a more aggressive histology.

Table S2. Demographics and Baseline Disease Characteristics.

	Ibrutinib (N=195)	Ofatumumab (N=196)
Age (years)		
Mean (SD)	66 (10)	67 (9)
Median	67	67
Min, max	30, 86	37, 88
<65 years, n (%)	77 (40)	75 (38)
≥65 years, n (%)	118 (61)	121 (62)
Gender, n (%)		
Male	129 (66)	137 (70)
Female	66 (34)	59 (30)
Race, n (%)		
Asian	3 (2)	2 (1)
Black or African American	8 (4)	9 (5)
White	174 (89)	177 (90)
Multiple	1 (1)	0 (0)
Patient declined to answer	9 (5)	8 (4)
Months from initial diagnosis to randomization		
Median	92	91
Min, max	5, 329	6, 346
Histology at diagnosis, n (%)		
CLL	185 (95)	188 (96)
SLL	10 (5)	8 (4)
Rai stage at screening, n (%)		
Stage 0	5 (3)	2 (1)
Stage I	51 (26)	42 (21)
Stage II	30 (15)	39 (20)
Stage III	23 (12)	35 (18)
Stage IV	86 (44)	78 (40)
Binet stage at screening, n (%)		
A	36 (18)	35 (18)
B	57 (29)	57 (29)
C	102 (52)	104 (53)
Baseline Eastern Cooperative Oncology Group performance status, n (%)		
0	79 (41)	80 (41)
1	116 (59)	116 (59)

	Ibrutinib (N=195)	Ofatumumab (N=196)
Bulky disease, n (%)		
<5 cm	71 (36)	92 (47)
≥5 cm	124 (64)	101 (52)
Missing	0 (0)	3 (2)
Chromosome abnormalities based on local laboratory results, n (%)		
Del11q		
Yes	63 (32)	59 (30)
No	127 (65)	132 (67)
Not reported	5 (3)	5 (3)
Del17p, n (%)		
Yes	63 (32)	64 (33)
No	132 (68)	132 (67)
Cytopenia (ANC ≤1.5 × 10^9/L, Hemoglobin ≤11g/dl, or Platelets ≤100 × 10^9/L), n (%)	124 (64)	123 (63)
ANC ≤1.5 × 10^9/L, n (%)	41 (21)	38 (19)
Hemoglobin ≤11 g/dl, n (%)	89 (46)	86 (44)
Platelets ≤100 × 10^9/L, n (%)	74 (38)	64 (33)

SD indicates standard deviation; ANC, absolute neutrophil count.

Table S3. Serious Adverse Events*.

System Organ Class MedDRA Preferred Term	Ibrutinib (N=195) n (%)	Ofatumumab (N=191) n (%)
Number of subjects reporting at least one SAE	81 (42)	58 (30)
Blood and lymphatic system disorders	8 (4)	11 (6)
Febrile neutropenia	3 (2)	4 (2)
Anemia	2 (1)	4 (2)
Cardiac disorders	13 (7)	6 (3)
Atrial fibrillation	6 (3)	1 (1)
General disorders and administration site conditions	12 (6)	4 (2)
Pyrexia	6 (3)	4 (2)
Infections and infestations	46 (24)	39 (20)
Pneumonia	17 (9)	12 (6)
Lung infection	5 (3)	0 (0)
Lower respiratory tract infection	4 (2)	2 (1)
Urinary tract infection	4 (2)	0 (0)
Upper respiratory tract infection	1 (1)	4 (2)

* Serious adverse events (SAEs) with subject incidence of ≥2% in either arm by system organ class and preferred term (safety population).

Table S4. Rate of Severe Infections (≥Grade 3).

Infections ≥Grade 3	Ibrutinib (N=195) n (%)	Ofatumumab (N=191) n (%)
Any ≥grade 3 infection	**47 (24)**	**42 (22)**
Upper respiratory tract infection	1 (1)	4 (2)
Pneumonia*	16 (8)	14 (7)
Urinary tract infection	7 (4)	1 (1)
Cellulitis	4 (2)	1 (1)
Lower respiratory tract infection	2 (1)	2 (1)
Bronchopulmonary aspergillosis	2 (1)	0 (0)
Herpes zoster	1 (1)	3 (2)
Sepsis	2 (1)	2 (1)
Respiratory tract infection	0 (0)	4 (2)
Stenotrophomonas infection	0 (0)	2 (1)
Grade 5	**6 (3)**	**9 (5)**

* Including *Pseudomonas aeruginosa.*

Table S5. Disposition of Study Population.

Study Treatment Phase Disposition	Ibrutinib (N=195) n (%)	Ofatumumab (N=196) n (%)
Did not receive study drug	0 (0)	5 (3)
Discontinued/completed	27 (14)	190 (97)
Ongoing	168 (86)	1 (1)
Primary reason for discontinuation of study treatment phase		
Progressive disease*	9 (5)	38 (19)
Adverse event/unacceptable toxicity	8 (4)	7 (4)
Withdrawal from treatment by patient	1 (1)	6 (3)
Deaths	8 (4)	9 (5)
Investigator decision	1 (1)	11 (6)
Withdrawal due to a new anticancer therapy (stem-cell transplant)	0 (0)	1 (1)
Withdrawal due to a new anticancer therapy (not stem-cell transplant)	0 (0)	3 (2)
Other	1 (1)	7 (4)
Completion of treatment regimen (ofatumumab treatment arm only)	0 (0)	119 (61)

* Investigator assessed.